

Risk of NSAID-Associated Gastro-Intestinal Complications

NSAID Series, P3

October 2003

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Introduction

Affecting approximately 37.9 million people, arthritis and other musculoskeletal conditions are among the most common chronic conditions in the United States. The two primary musculoskeletal conditions are osteoarthritis (OA) and rheumatoid arthritis (RA). Some 16-20 million people in the United States are estimated to have OA, which is comparable to the number of patients with diabetes. Approximately 2.5 million persons in the United States are estimated to have RA. Musculoskeletal conditions have been reported to account for 12% of total health care expenditures, with arthritis alone accounting for 4% [1]. By the year 2020, it is expected that 58.4 million people will suffer from these diseases [2].

Although patients with musculoskeletal conditions represent less than 20% of the U.S. population, they account for almost one-third (29.7%) of all physician office visits and 32.7% of all hospital admissions annually [1]. Drug therapy has improved in alleviating many of the symptoms of these two chronic conditions; however, drugs do not halt the disease progression. Drug-related problems are common and can significantly limit patient progress, but with the advent of Cox-2 inhibitors, interleukin-1 antagonists, and tumor necrosis factor (TNF) modulators, physicians have an expanding armamentarium of drugs for osteoarthritis and rheumatoid arthritis.

The average cost of treating OA was estimated at just under \$550 per patient per year. The cost of ambulatory care was \$110; medications (\$173 per person) represented about one-third of expenditures, of which almost half was spent to protect against the GI complications of NSAID treatment. The cost and treatment profile of RA is considerably different [3]. In 1992, the annual cost of treating a patient with RA was \$2,162 per patient [3]. RA patients average 7.7 physician office visits per year—twice as many as for OA patients. Medications to protect against adverse GI effects consumed approximately 16% of the medication budget for RA patients [4].

NSAIDs are the common therapy link between OA and RA. In both conditions, NSAIDs provide symptom control but do not alter disease progression. In OA, NSAIDs are used in low doses for pain control; in RA, they may be used in low or high doses to manage both pain and inflammation. NSAIDs treat the symptoms of OA and RA by inhibiting the production of prostaglandins (PG), the mediators of pain and inflammation. NSAIDs inhibit PG production by blocking the enzyme cyclooxygenase (Cox). Unfortunately, inhibiting Cox has deleterious

effects on organ systems that require PG for normal functioning. Although most of the side effects associated with NSAID therapy are mild and abate when therapy is discontinued, GI side effects can be more serious.

NSAID Associated GI Complications

It has been estimated that up to 20% of patients on NSAIDs experience GI problems.[5] When compared to nonusers, NSAID users are at nearly three times greater risk for developing gastric ulcerations, bleeding, and death from these complications. The Food and Drug Administration (FDA) estimates that these GI complications cause between 10,000 and 20,000 deaths and approximately 76,000 hospitalizations annually.[6]

The damage that NSAIDs inflict on the GI tract occurs in two ways. Direct mucosal injury can occur when a drug, such as aspirin, causes mucosal erosions or hemorrhages, which can be locally irritating. Inhibiting endogenous gastric PG synthesis, specifically Cox-1, significantly increases the likelihood of mucosal injury. Naturally occurring PGs like Cox-1 and Cox-2 are important in the production of gastric bicarbonate and mucous-key components of the stomach's protective barrier—and in the maintenance of submucosal blood flow.

One of the dangers associated with NSAID-induced gastric ulcers is that most patients remain asymptomatic until complications arise. Approximately 81% of the serious GI complications with NSAIDs occur asymptotically.[5] Although perforation can occur within a few days of the initiation of therapy, most complications occur during chronic NSAID use. Taking NSAIDs with food does not appear to reduce the overall risk of ulceration; however, food may help decrease the direct mucosal irritation.

Risk Factors for NSAID Associated GI Complications

Knowledge of risk factors of NSAID associated GI complications is important in selecting therapy and/or implementing prophylaxis in those patients at highest risk thus minimizing the likelihood of GI complications. The literature contains original research and reviews that identify factors associated with negative GI outcomes. These risk factors will be discussed below and are summarized in Table 1.

- One of the most frequently cited and of primary importance is a history of peptic ulcer disease, whether caused by NSAIDs or *Helicobacter pylori*. [7-13] The risk is even higher for individuals who have had an upper GI bleed associated with an ulcer. [7-11, 14-16]
- Patients receiving concurrent anticoagulation therapy, such as warfarin, are at increased risk. [7-11]
- Concomitant therapy with corticosteroids has been shown to double the risk of gastropathy. [7-12, 14, 15]
- Age itself is an independent risk factor. As individuals advance in age from 65 to 85, their risk of NSAID-related ulcers increases exponentially.[12, 14-16]

- GI complications have been shown to be NSAID-dose dependent such that those taking high doses of a single agent or multiple NSAIDs are at greater risk.[11, 12] The dose-response is so strong that its effect is probably more important than any between-drug differences.[17]
- Although not frequently cited, poor general health has also been found to be a risk factor for NSAID-associated GI complication.[15, 16]
- It should also be noted that the effects of drugs are synergistic—combinations of NSAIDs with anti-coagulants and corticosteroids put patients at higher risk.[17]
- Research has shown that the use of misoprostal offers cytoprotection from NSAIDs such that nonuse of this agent could be considered a risk factor for GI complication.[11, 18] It should be noted, however, that the cited research studies were conducted prior to the introduction of Cox-2s and thus do not compare misoprostal with Cox-2s.
- Recent information from several studies suggests that a combination of risk factors magnified the potential for NSAID-associated ulcers and other serious complications.[11]
- Concurrent use of H₂ receptor antagonists (H₂RA), proton pump inhibitors (PPI) and antacids has also been cited as a risk factor[5, 19, 20]. (Although it would seem that use of these agents is a result of NSAID use and their GI toxicity, the authors offered some explanations. One explanation is that H₂RAs, PPIs and antacids are used and thus identify those at highest risk for GI complications. Another possible explanation is that they may mask the GI damage occurring and thus contribute to a more severe GI outcome.[19])

Other factors that have been mentioned as risk factors include: history of alcohol abuse, *H. pylori* infection and male gender. [13, 14, 28] Interestingly, one study which looked at numerous risk factors found that smoking was not a risk factor for NSAID associated GI complications. [13]

Table 1. Risk Factors for NSAID Associated GI Complications

History of peptic ulcer disease
History of GI bleed associated with ulcer
Concurrent anticoagulation therapy
Concurrent antiplatelet therapy
Age
Higher NSAID dose
Traditional NSAID (versus Cox-2)
Concurrent therapy with H ₂ A, PPI or antacid
Possible Risk Factors
<i>H. pylori</i> infection
Alcohol abuse
Male gender

Traditional NSAIDs versus Cox-2s

When introduced, the Cox-2s were marketed as relatively “safe” NSAIDs with significantly fewer GI complications when compared to traditional NSAIDs. Four coxib outcomes studies (VIGOR, ADVANTAGE, CLASS, AND SUCCESS) were conducted in over 39,000 patients with osteoarthritis and rheumatoid arthritis. These studies showed that the Cox-2-specific inhibitors, rofecoxib and celecoxib, resulted in significantly fewer clinically important upper GI adverse events than did non-selective NSAIDs, while having similar efficacy.[21, 22] Other research has also shown similar results, that treatment with celecoxib was as effective as treatment with diclofenac plus omeprazole, with respect to the prevention of recurrent bleeding.[23] And, that treatment with celecoxib was associated with a lower risk of endoscopic ulcers when compared with diclofenac or ibuprofen [24] Recently, these claims of safety have been questioned suggesting that further long-term outcomes trials appear necessary.[25-27]

Analysis of NSAID Associated Risk Factors in the LA Medicaid Program

To determine which of the known risk factors have a significant association with NSAID related GI complications in the Louisiana Medicaid population, a retrospective claims data analysis was performed.

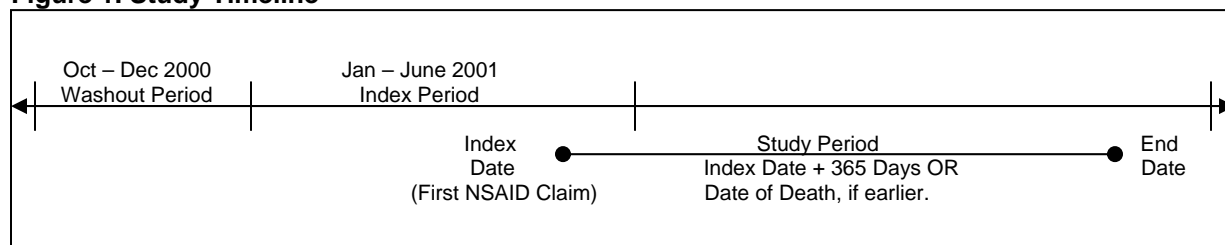
Study Methodology

Louisiana Medicaid claims were analyzed to identify risk factors associated with gastric complications in arthritis recipients on NSAID (including Cox-2) drug therapy. Paid claims for recipients diagnosed with osteoarthritis who had received at least three prescriptions for an NSAID, including Cox-2s, were included in the study.

Only newly treated recipients were included in the study group. To be classified as newly treated, recipients must not have had an NSAID claim during the three-month washout period of October through December of 2000. The index period was January through June of 2001. The study period for each recipient began on the date of their first claim during the index period (index date). The claims for each recipient were then analyzed for the period from the index date until the earlier of the following dates (See Figure 1):

- Index date + 365 days.
- Date of death, as identified through eligibility records.

Figure 1. Study Timeline



The inclusion criteria used to select recipients for the study were:

- At least one claim for osteoarthritis (ICD-9-CM 715.xx) during the index period.
- At least three claims for an NSAID, including Cox-2s, during the study period.
- No NSAID claim during the washout period.
- Continuous eligibility from beginning of washout period through end of study period.

In order to determine the risk factors for GI complications, a logistic regression analysis was performed. The model used the presence or absence of a GI event as the dependent variable and the risk factors as the independent variables (see Appendix 1).

Results

A total of 1866 recipients with osteoarthritis who were on NSAID/Cox-2 therapy met the inclusion criteria. Of this study group, 241 recipients (12.9%) experienced an adverse GI outcome during the study period. A severe GI complication (resulting in inpatient hospitalization) was identified in 60 of these recipients who experienced a GI event. The remaining 181 recipients had only minor GI complications (outpatient claims only).

Results of the logistic regression analysis in Tables 2 and 3 show that poor general health was the predominant risk factor for a GI event (either severe or minor). Recipients in poor health were 2.7 times more likely to experience a gastric complication while taking an NSAID or Cox-2 than were recipients in better health. Anti-platelet use, older age, and the number of days of steroid use were found to be additional risk factors associated with a severe GI event. A prior history of GI complications was also found to have a significant association with minor GI complications.

Table 2. Summary of Risk Factors for GI Complications in Recipients on NSAID/Cox-2 Therapy

Variable	Any GI Complications	Severe GI Complications	Minor GI Complications
Poor Health	X	X	X
Anti-platelet Use	X	X	
GI History	X		X
Older Age		X	
Steroid Days		X	

Table 3. Detail of Risk Factors for GI Complications in Recipients on NSAID/Cox-2 Therapy

Variable	Risk Factors for Any GI Event			Risk Factors for Severe GI Event			Risk Factors for Minor GI Event		
	Parameter Estimate	Probability	Odds Ratio	Parameter Estimate	Probability	Odds Ratio	Parameter Estimate	Probability	Odds Ratio
Intercept	-2.3544	<.0001		-4.4083	<.0001		-2.5749	<.0001	
Poor Health	0.9968	<.0001	2.710	1.1646	<.0001	3.205	0.8609	<.0001	2.365
Anti-platelet Use	0.5397	0.0057	1.715	0.7645	0.0177	2.148			
GI History	0.6557	0.0069	1.926				0.8324	0.001	2.299
Older Age				0.637	0.0251	1.891			
Steroid Days				0.0039	0.0214	1.004			

Note: The variable for proton pump inhibitor (PPI) use was excluded from the model after the preliminary run because of its use in treatment of GI events. PPI use was significantly associated with GI events masking the significance of concurrent use of a PPI as a risk factor.

Upon examination of the length of time during the study period that a steroid was taken concurrently with an NSAID or Cox-2 (see Table 4), it was found that the average steroid days supply for steroid users with a severe GI outcome was nearly twice as high as the average steroid days supply for steroid users with no GI outcome. Steroid users with a minor GI outcome had an average of 30 days supply of a steroid during the study period. During the analysis of other continuous variables (Steroid dose, NSAID/Cox-2 dose, and NSAID/Cox-2 days) no major differences were identified between recipients who experienced minor, severe, or no GI events.

Table 4. Means of Continuous Variables by Outcome

	Severe GI Event		Minor GI Event		No GI Event	
	Per Eligible Recipient	Per User	Per Eligible Recipient	Per User	Per Eligible Recipient	Per User
Number of Recipients (NSAID Users)	60		181		1,625	
Number of Steroid Users	21		49		398	
Average NSAID Dose (All Eligible Recipients were Users)	0.96	0.96	1.05	1.05	1.06	1.06
Average NSAID Days (All Eligible Recipients were Users)	185.47	185.47	181.57	181.57	186.89	186.89
Average Steroid Dose	0.07	0.19	0.08	0.31	0.05	0.20
Average Steroid Days	29.65	84.71	8.12	30.00	10.56	43.13

In Table 5, the recipients were classified into one of the following categories:

- Recipients on traditional NSAID drug therapy only (No Cox-2 drugs).
- Recipients on Cox-2 drug therapy only (No traditional NSAIDs).
- Recipients who took both traditional NSAID and Cox-2 drugs during the study period.

An analysis of the three groups found no major differences in GI outcomes based on the type of NSAID drugs utilized during the study period.

Table 5. Drug Therapy Distribution by GI Outcome

	Severe GI		Minor GI		No GI		Total
	Number	% of Total	Number	% of Total	Number	% of Total	
100% Traditional NSAID Therapy	10	3.9%	19	7.5%	226	88.6%	255
100% Cox-2 Therapy	33	3.9%	71	8.4%	741	87.7%	845
Combination NSAID/Cox-2 Therapy	17	2.2%	91	11.9%	658	85.9%	766

Figures 2 and 3 show various demographic distributions by GI outcome. In Figure 2, a higher percentage of recipients who experienced a severe GI outcome were older (65+) or in poor health than recipients who experienced only a minor or no adverse GI outcome.

Figure 2.

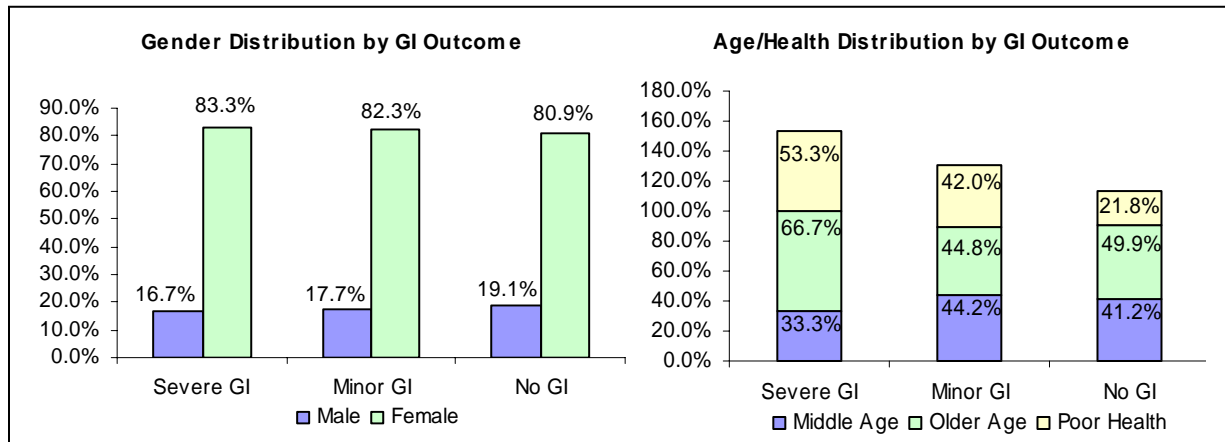
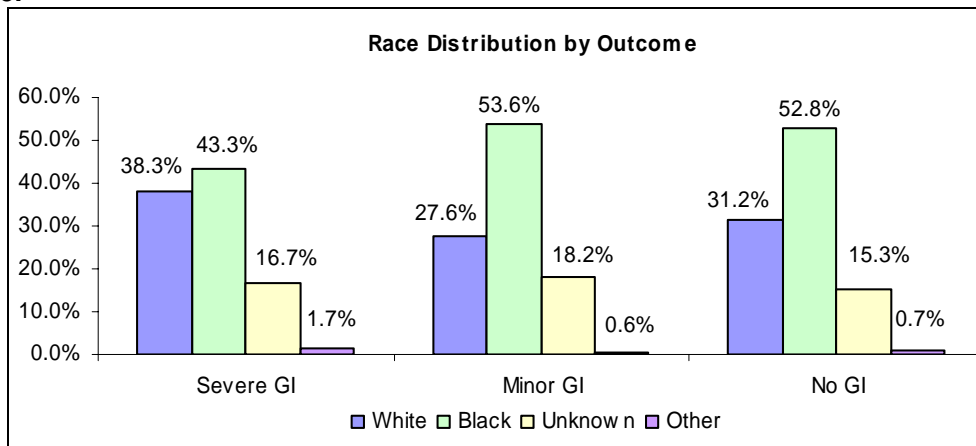


Figure 3.



Discussion and Conclusion

Gastrointestinal (GI) toxicity is a major limiting factor in the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Complications of ulcer disease, *i.e.*, hemorrhage and perforation, occur far more often in patients taking these agents than in comparable control groups. The overall risk for serious adverse gastrointestinal (GI) events in Louisiana Medicaid patients in poor health taking NSAIDs is 2.7 times greater than that of NSAID users not in poor health. In elderly patients (>65yr), this risk is approximately two times that of non-elderly. Patients who have a history of peptic ulcer disease or other GI illness are at a 2-time greater risk of developing a serious GI complication while on NSAID therapy. Estimates of the incidence rate of GI adverse effects associated with NSAIDs have reached as high as 20%. This incidence rate is constant for every year of therapy. Although most of these adverse effects are classified as dyspepsia, there are a menacing number of “silent” GI bleeds occurring in NSAID-treated patients. The appearance of this “silent-killer” is unpredictable and is often asymptomatic.

Approximately 20 million patients in the U.S. take NSAIDs on a regular basis. Thus, it is obvious that the morbidity and costs associated with GI complications of NSAID use are significant. On the other hand, the costs of providing prophylactic therapy to all patients to

prevent NSAID-induced ulcers and bleeding are prohibitive. Healthcare professionals can play an important role in reducing the incidence of drug-induced GI disorders by identifying “at risk” patients, alerting them to the early warning signs and providing education to help prevent these effects. Table 1 lists risk factors found in the literature for GI complications associated with NSAIDs. Table 2 summarizes the risk factors identified in the Louisiana Medicaid population.

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Appendix 1. Logistic Regression Model

GI Event		=	Risk Factors	
Dependent Variable			Independent Variable	
Name	Description		Name	Description
Severe GI	Recipient with an inpatient GI claim with a diagnosis of 531.xx - 533.xx, 535.0x, 535.5x, or 578.xx.		NSAID Only Recips	Recipients taking an NSAID (including Cox-2s) with the percentage of the number of traditional NSAID prescriptions* divided by the number of Cox-2* prescriptions greater than or equal to 60% during the study period.
Minor GI	Recipient with an outpatient, long term care, or physician GI claim (no inpatient claims) with a diagnosis of 531.xx - 533.xx, 535.0x, 535.5x, or 578.xx.		C2 Only Recips	Recipients taking an NSAID (including Cox-2s) with the percentage of the number of traditional NSAID prescriptions* divided by the number of traditional NSAID* prescriptions greater than or equal to 60% during the study period.
Any GI	Recipient classified as having either a minor or severe GI event.		NSAID C2 Combined Recips	Recipients taking an NSAID (including Cox-2s) with a the percentage of the number of traditional NSAID prescriptions* divided by the number of Cox-2* prescriptions (and vice versa) less than 60% during the study period.
			SDAYS	Total steroid days supply during study period.
			SDOSE	Steroid dose expressed as a percentage of the maximum recommended dose. It was calculated by multiplying quantity by strength, then dividing by days supply to obtain average daily dose. The average daily dose was then expressed as percentage of the maximum recommended daily dose.
			NDAYS	Total NSAID (including Cox-2s) days supply during study period.
			NDOSE	NSAID (including Cox-2s) dose expressed as a percentage of the maximum recommended dose. It was calculated by multiplying quantity by strength, then dividing by days supply to obtain average daily dose. The average daily dose was then expressed as percentage of the maximum recommended daily dose.
			LTC Recips	Recipients with at least 2 claims for long term care during study period
			Misopros Recips	At least one claim for Misoprostol* during study period.
			Poor Hlth Recips	Recipients in the 75th percentile of the number of ICD-9-CM diagnoses during the study period.
			GI Hist Recips	Recipients with a claim with a GI diagnosis (531.xx - 533.xx, 535.0x, 535.5x, 578.xx) or for a proton pump inhibitor (PPI)* or H2-Agonist (H2A)* drug during the washout period.
			CVD Hist Recips	Recipients with a claim with a cardiovascular disease diagnosis (410.xx - 416.xx or 434.xx - 436.xx) during the washout period.
			Anti Coag Recips	Recipients with a claim for an anti-coagulant drug* during the study period.
			PPI Recips	Recipients with a claim for a proton pump inhibitor (PPI)* drug during the study period.
			Anti Plt Recips	Recipients with a claim for an anti-platelet* drug during the study period.
			Steroid Recips	Recipients with a claim for a steroid* (not inhaled or topical) during the study period.
			Middle Age	Age at index date between 40 and 64
			Older Age	Age at index date 65+
			Afam	African American
			Minor	Other Minority
			Female	Female

*Note - For a list of drugs, see Appendix 2.

Appendix 2. Drug Names and HICL Numbers

NSAID

Aspirin—001820
Diclofenac—008824, 003733
Diclofenac/Misoprostol—008302
Diflunisal—001847
Etodolac—006089
Fenoprofen—003724
Flurbiprofen—003728
Ibuprofen—003723
Indomethacin—003719, 003718
Ketoprofen—003736
Meclofenamate—003730
Meloxicam—012181
Nabumetone—006311
Naproxen—003727, 003726
Oxaprozin—006620
Piroxicam--003732
Sulindac—003729
Tolmetin—003725
Mefenamic Acid – 001776
Ketorolac – 005175

Cox-2

Celecoxib—018975, 018979
Rofecoxib—020208
Valdecoxib—023223

Misoprostol

Misoprostol--001187
Arthrotec--008302

Steroid

Betamethasone – 002884
Betamethasone Sodium Phosphate—002882
Budisonide—006545
Cortisone Acetate—002860
Dexamethasone—002889
Dexamethasone Acetate—002886
Dexamethasone Phosphate—002887
Dexamethasone Sodium Phosphate—002888
Fludrocortisone Acetate—002899
Hydrocortisone—002867
Hydrocortisone Acetate—002863
Hydrocortisone Cypionate—002864
Hydrocortisone Sodium Phosphate—002865
Hydrocortisone Sodium Succinate—002866
Methylprednisolone—002877
Methylprednisolone Acetate—002875
Methylprednisolone Sodium Succinate—002876
Prednisolone—002874
Prednisolone Acetate—002870, 003479
Prednisolone Sodium Phosphate—002871
Prednisolone Tebutate—002873
Prednisone—002879
Triamcinolone—002894
Triamcinolone Acetonide—002891
Triamcinolone Diacetate—002892
Triamcinolone Hexacetonide—002893

Anti-Coagulant

Anti-thrombin—005735
Argatroban—021768
Bivalirudin—021872
Dalteparin Sodium—007429
Danaparoid Sodium—010155
Enoxaparin Sodium—007878
Fondaparinux Sodium—023233
Heparin Sodium—002810, 009545, 002810, 002808
Leipirudin—018277
Tinzaparin Sodium—008989

H2-Agonist

Cimetidine—004518, 009793, 009842
Cimetidine HCL/NACL--004517
Famotidine—004521
Famotidine/NACL--008965
Histamine—010084
Histamine Phosphate—004477,009584
Nizatidine—004522
Ranitidine HCL—004520,022857
Ranitidine HCL/NACL--004519

Proton Pump Inhibitor

Esomeprazole Mag Trihydrate—021607
Lansoprazole/Amox—008993
Lansoprazole/Amox Tr/Clarith —017026
Omeprazole—004673
Pantoprazole Sod Sesquihydrate—011590
Pantoprazole Sodium—022009
Rabeprazole Sodium—018847

Anti-Platelet

Abciximab—009655
Anagrelide HCL—012902
Cilostazol—017433
Clopidogrel Bisulfate—017539
Dipyridamole—000168, 013230, 019803
Eptifibatide—018422
Ticlopidine HCL—006232
Tirofiban HCL M-Hydrate—018386
Trenprostiniil Sodium—023651